

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2004/009690

International filing date (day/month/year)
31.08.2004

Priority date (day/month/year)
01.09.2003

International Patent Classification (IPC) or both national classification and IPC
C07D333/20, C07D307/52

Applicant
LONZA AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

001569324
International application No.
PCT/EP2004/009690

APPROVED 22 FEB 2006

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/009690

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 12

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 12
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/009690

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-11	✓
	No: Claims		
Inventive step (IS)	Yes: Claims		
	No: Claims	1-11	
Industrial applicability (IA)	Yes: Claims	1-11	
	No: Claims		

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

20040621 17
PCT/EP2004/009690
23 FEB 2006
International application No.

PCT/EP2004/009690

- 1) The present application relates to the preparation of chiral compounds of formula I by asymmetric hydrogenation of ketones of formula II in the presence of a transition metal complex with a chiral bidentate phosphine ligand (claims 1-11). Furthermore, certain compounds of formula I are claimed (claim 12). In view of a finding of non-unity, the following observations concern only the subject-matter of claims 1-11.
- 2) The following documents are referred to
D1: WO 03 062219 A
D2: WO 03 061825 A
D3: WO 03 061826 A
D4: ORGANIC LETTERS, vol. 2, no. 12, 2000, pages 1749-1751,
D5: CHEM, PHARM. BULL. vol. 43, no. 5, 1995, pages 748-753,
D6: WO 02 10113 A
- 3) Novelty
The claimed matter may be acknowledged novelty:
Document D1 describes a process for obtaining a compound of formula I by resolving the racemic compound.
Documents D2-D4 describe the asymmetric hydrogenation of ketones in the presence of a transition metal complex with a chiral bidentate phosphine ligand and a diamine; the ketones of formula II are not specifically mentioned.
Documents D5 and D6 describe the asymmetric hydrogenation of ketones in the presence of a transition metal complex with a chiral bidentate phosphine ligand; the ketones of formula II are not mentioned.
- 4) Inventive step
In view of Document D1 the problem to be solved may be seen in the provision of an alternative method for providing enantiomerically pure compounds of formula I. As solution to this problem the claimed matter would at present seem obvious to the person skilled in the art. Asymmetric synthesis is well established as alternative to resolving methods. The person skilled in the art would therefore consider application of successful approaches for asymmetric synthesis of structurally related compounds such as described in documents D2-D5, in which the asymmetric hydrogenation of

related ketones in the presence of a transition metal complex with a chiral bidentate phosphine ligand with (D2-D4) or without (D5) diamines is described.